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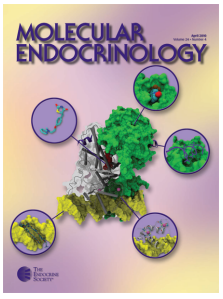

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Diagnosis and Treatment of Subclinical Hypercortisolism

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Context: Subclinical hypercortisolism (SH) is a condition of biochemical cortisol excess without the classical signs or symptoms of overt hypercortisolism. It is thought to be present in the 5–30% of patients with incidentally discovered adrenal mass (adrenal incidentalomas), which in turn are found in 4–7% of the adult population. Therefore, SH has been suggested to be present in 0.2–2.0% of the adult population. Some studies suggested that this condition is present in 1–10% of patients with diabetes or established osteoporosis. The present manuscript reviews the literature on diagnostic procedures and the metabolic effect of the recovery from SH.

Evidence Acquisition: A PubMed search was used to identify the available studies. The most relevant studies from 1992 to November 2010 have been included in the review.

Evidence Synthesis: The available data suggest that SH may be associated with chronic complications, such as hypertension, diabetes mellitus, overweight/obesity, and osteoporosis. The available intervention studies suggest that the recovery from SH may lead to the improvement of hypertension and diabetes mellitus. A retrospective study suggests that this beneficial effect could be predicted before surgery.

Conclusions: SH is suggested to be associated with some chronic complications of overt cortisol excess. Recovery from this condition seems to improve these complications. However, a large, prospective, randomized study is needed to confirm this hypothesis and to establish the best diagnostic approach to identify patients with adrenal incidentalomas who can benefit from surgery. **(*J Clin Endocrinol Metab* 96: 1223–1236, 2011)**

Subclinical hypercortisolism (SH) is defined as a status of altered hypothalamic-pituitary-adrenal (HPA) axis secretion in the absence of the classical signs or symptoms of overt cortisol excess (1, 2). The diagnosis and treatment of SH have recently become a topic of growing interest and are currently under debate (3, 4). The interest in SH is due to its high prevalence. Indeed, SH is estimated to be present in 5–30% of patients with adrenal masses serendipitously found by imaging for unrelated diseases [adrenal incidentalomas (AI)] (1, 5). Because AI are thought to be present in up to 4–7% of adults (6–11), the prevalence of SH in this population may be estimated to be between 0.2 and 2.0% (2).

The term "subclinical hypercortisolism" has been preferred to that of "preclinical" or "subclinical Cushing syndrome" because the progression toward overt clinical hypercortisolism is very rare (11–13). However, although SH by definition is not associated with signs and/or symptoms specific to overt cortisol excess, such as purple striae, easy bruising, proximal muscle weakness, and plethora (14), some evidence suggests that this condition may lead to long-term consequences of cortisol excess (*i.e.* diabetes, hypertension, obesity, and osteoporosis) (15–21). These conditions, however, are not specific to cortisol excess, being highly frequent in the general population. Thus, even if the concomitant presence in the same individual of

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Abbreviations: AI, Adrenal incidentaloma; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; HbA1C, glycated hemoglobin; HPA, hypothalamic-pituitary-adrenal; LDDST, low-dose DST; MSaC, midnight salivary cortisol; MSeC, midnight serum cortisol; SH, subclinical hypercortisolism; UFC, urinary free cortisol.

all these possible consequences of cortisol excess may suggest the presence of SH, in the absence of specific signs or symptoms of hypercortisolism but in the presence of biochemical abnormalities of HPA axis, the term "subclinical hypercortisolism" may be adequate.

This clinical review will summarize the available data regarding the diagnostic approach, prevalence, and management of SH.

Diagnosis of SH

Pitfalls in the diagnosis of SH

Although the above-reported definition of SH is extensively used and accepted, there is no consensus yet on the clinical and/or biochemical criteria to diagnose this condition.

The diagnosis of SH is a challenge for clinicians due to several causes. First, particularly in AI patients, cortisol secretion is a continuum from completely normal to clearly increased levels, and it is highly variable in the same individual (3, 22). Therefore, diagnosing SH by arbitrary cutoffs of indexes of cortisol secretion leads to unavoidable mistakes in classifying some patients.

Second, the reliability of almost all markers of HPA axis activity, particularly ACTH and 24-h urinary free cortisol (UFC), is low (3, 14, 23), and several comorbidities (*i.e.* type 2 diabetes and obesity) and concomitant medications may affect the result of the dexamethasone suppression test (DST) (24).

Finally, because SH by definition is not characterized by a specific clinical picture, a clinical "gold standard" for diagnosing SH is lacking. As a consequence, the identification of subtle signs of cortisol excess depends mainly on the personal practice of the physician and may, therefore, be overlooked by those with less expertise with hypercortisolemic patients. However, in our and other authors' experience (1), the presence of signs and/or symptoms of cortisol excess is extremely rare in patients referred for the presence of an AI. On the other hand, it has become increasingly evident that the glucocorticoid sensitivity may be different among the different individuals and among the different tissues in the same individual, due also to polymorphisms of both glucocorticoid receptor (25–28) and 11β-hydroxysteroid-dehydrogenase type 1 genes (29, 30).

Alterations of HPA axis activity parameters in patients with AI

The majority of the studies regarding the diagnosis and the treatment of SH have been focused on series of patients with AI. The above-mentioned pitfalls explain the discordant data about the prevalence of SH in these patients (9, 17–19, 21, 22, 31–62). Several alterations of HPA axis secretion have been reported in AI patients, whose frequencies vary among the different series. In more than 25% of AI subjects, the lack of cortisol suppression after 1- or 3-mg overnight DST or 2-d low-dose DST (LDDST) (19, 34, 41, 44, 46, 48, 53, 55, 56, 60, 61), elevated UFC levels (21, 43, 48, 49, 53, 60, 63), loss of cortisol secretion circadian rhythm (22, 44, 48, 56, 60), altered cortisol and ACTH response to CRH stimulation (37, 38, 46), low basal ACTH (19, 21, 32, 36, 40, 43, 44, 48, 49, 56, 60, 61), and dehydroepiandrosterone sulfate (DHEAS) (35–38, 41) levels are present, suggesting the presence of SH (Table 1).

The frequency of altered 1-mg or 3-mg DST in AI patients varies among the different studies, ranging from 3.0 to 100% on the basis of the cutoff, dexamethasone doses, and modality of execution (Table 1). To date, the 1-mg DST is the most used test to diagnose SH, either alone (34–36, 38, 44–46) or in combination with other parameters (9, 18, 21, 32, 37, 39, 42, 49, 52–54, 56, 60, 61). Nonetheless, the 1-mg DST cutoff is still a matter of debate. The National Institutes of Health State-of-the-Science Conference (64) and the American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of AI (65) recommend the cutoff of 5 μg/dl (138 nmol/liter) as the normal level of cortisol suppression in patients with suspected SH. The reason to screen for SH with a higher cutoff than that recommended for overt cortisol excess [1.8 μg/dl (50 nmol/liter)] (66) is that in patients without signs or symptoms suggestive of hypercortisolism, the *a priori* possibility of having SH is estimated to be lower than that of a false-positive result (1). Thus, reducing the cutoff of 1-mg DST leads to a decrease in specificity and, therefore, to more false diagnosis of SH (65). Several studies (19, 21, 32, 34, 38, 39, 44, 46, 49, 53, 60, 61, 67) and recently the French Society for Endocrinology (68), however, have proposed a lower cutoff to increase sensitivity. On the contrary, to increase specificity, some authors have proposed higher (3 or 8 mg) dexamethasone doses (40, 46, 54, 56), which however did not show a better performance (14, 23, 66). Similarly, LDDST has been used to diagnose SH (18, 40, 41, 55) without advantages, with the exception of patients affected with alcoholism, psychiatric disorders, and diabetes in whom this test may be more accurate (1, 14, 66). Because LDDST is cumbersome and not easy to be performed, it is generally used as a confirmatory test (1, 14). In the author's opinion, the use of the cutoff of 3.0 μg/dl (83 nmol/liter) for the 1-mg DST test represents the best compromise between sensitivity and specificity for screening for SH because it

TABLE 1. Alterations of the HPA axis secretion in patients with AI

First author, year (Ref.)	No. of patients	CRH (%)	CCR (%)	ACTH (%)	UFC (%)	DST (%)	DEX dose, DST cutoff	SH criteria	SH (%)
Reincke, 1992 (34)	68	7.5	n.a	11.8	4.4	21.6	1 mg, 3 μg/dl	DST	12
Osella, 1994 (35)	45	22	n.a	n.a.	2	15	1 mg, 5 μg/dl	DST	16
Flecchia, 1995 (36)	24	n.a.	n.a	25	21	17	1 mg, 5 μg/dl	DST	29
Ambrosi, 1995 (37)	32	33	n.a.	12.5	12.5	13.7	1 mg, 5 μg/dl	DST plus ≥1 out of CRH, CCR, ACTH, UFC	12
Bardet, 1996 (38)	35	33	n.a.	21	11	13	1 mg, 3.5 μg/dl	DST	8.5
Bondanelli, 1997 (39)	38	8	n.a.	18	2.6	10	1 mg, 3.5 μg/dl	DST plus ACTH	10.5
Kasperlik-Zeluska, 1997 (40)	208	17	n.a.	34	5.2	3[a]	LDDST, 2 mg/24 h[a]	DST plus HDDST	2.9
Tsagarakis, 1998 (41)	61	n.a.	n.a	n.a.	n.a.	25	LDDST, 2.5 μg/dl	DST	25
Terzolo, 1998 (42)	53	n.a.	n.a.	9.4	7.5	17	1 mg, 5 μg/dl	DST plus UFC	6
Torlontano, 1999 (43)	32	n.a.	n.a.	65.6	25	9.4	1 mg, 5 μg/dl	UFC	25
Rossi, 2000 (18)	65	n.a.	12.3	23	17	25	LDDST, 3.0 μg/dl	DST plus ≥1 out of CRH, CCR, ACTH, UFC	18.5
Mantero, 2000 (9)	1004	17	17	15	11	10	1 mg, 5 μg/dl	≥2 out of CRH, CCR, ACTH, UFC, DST	9.2
Favia, 2000 (45)	158	n.a.	n.a.	n.a.	n.a.	5.1	1 mg, 5 μg/dl	DST[c]	5.1
Tanabe, 2001 (44)	38	13.1	28.9	26	n.a.	47.4	1 mg, 3 μg/dl	DST	47.4
Midorikawa, 2001 (46)	15	26.6	6.6	15	n.a.	26.6	1 mg, 3 μg/dl	DST or HDDST	26.6
Grossrubatscher, 2001 (47)	53	n.a.	n.a.	15	4[a]	11	1 mg, 5 μg/dl	DST plus ≥1 out of CRH, CCR, ACTH, UFC	5.7
Valli, 2001 (48)	31	n.a.	25.8	25.8	61	38.4	1 mg, 5 μg/dl	Unilateral uptake[d]	61.3
Chiodini, 2001 (49)	24	n.a.	n.a.	41.7	33.3	12.5	1 mg, 3 μg/dl	≥2 out of ACTH, UFC, DST	29
Libè, 2002 (52)	64	4.6	n.a.	10.9	9.4	18.7	1 mg, 5 μg/dl	≥2 out of CRH, CCR, ACTH, UFC, DST	18.8
Chiodini, 2002 (53)	38	n.a.	n.a.	23.7	42.1	28.9	1 mg, 3 μg/dl	≥2 out of ACTH, UFC, DST	34.2
Emral, 2003 (54)	70	n.a.	n.a.	n.a.	n.a.	5.7	3 mg, 3 μg/dl	DST and HDDST	5.7
Hadjidakis, 2003 (55)	42	n.a.	n.a.	n.a.	n.a.	43	LDDST, 2.5 μg/dl	LDDST	42.9
Chiodini, 2004 (19)[b]	70	n.a.	n.a.	57.1	20	28.5	1 mg, 3 μg/dl	≥2 out of ACTH, UFC, DST	30
Katabami, 2005 (56)	39	n.a.	73.5	46.6	n.a.	38.5	1 mg, 3 μg/dl	DST and HDDST	38.5
Terzolo, 2005 (22)	210	n.a.	29.4	9.7	10.8	13.8	1 mg, 5 μg/dl	n.a.	n.a.
Chiodini, 2009 (21)[b]	287	n.a.	n.a.	26.4	52.9	24.7	1 mg, 3 μg/dl	≥2 out of ACTH, UFC, DST	29.6
Masserini, 2009 (32)[b]	103	n.a.	14.6	50.5	12.6	24.3	1 mg, 3 μg/dl	≥2 out of ACTH, UFC, DST	21.4
Eller-Vainicher, 2010 (60)[b]	60	n.a.	48.3	63.3	31.7	53.3	1 mg, 3 μg/dl	≥3 out of CCR, ACTH, UFC, DST	48.3
Chiodini, 2010 (61)[b]	108	n.a.	n.a.	52.8	20	28.7	1 mg, 3 μg/dl	≥2 out of ACTH, UFC, DST	38

CRH, Blunted response to CRH; CCR, altered circadian cortisol rhythm (elevated MSeC or MSaC levels); ACTH, low ACTH levels [<10 pg/ml (2.2 pmol/liter)]; UFC, 24-h UFC levels above the upper limit of the normal range; DST, reduced cortisol suppression after a DST; DEX, dexamethasone; HDDST, high dose (8 mg) overnight DST; LDDST, 2-d low dose (2 mg/d) DST; n.a., data not available. SI conversion factors: cortisol × 27.56; ACTH × 0.22.

[a] 24-h urinary 17-hydroxycorticosteroids.

[b] Data provided by the authors but not reported in the papers.

[c] DST was performed in patients with increased morning serum cortisol levels.

[d] 131I-6b-iodomethyl norcholesterol scintigraphy.

has been substantiated on a clinical basis (19, 21, 32, 34, 44, 46, 48, 49, 53, 56, 58–61).

Few studies reported a high frequency (*i.e.* higher than 25%) of elevated UFC levels in patients with AI (21, 43, 48, 49, 53, 60). Generally, UFC is used in combination with other parameters to individuate patients with SH (9, 18, 19, 21, 32, 37, 42, 47, 49, 52, 53, 60, 61). This may be because UFC cannot reliably reveal a slight cortisol

excess (69, 70) and may also be due to the technical problems associated with its determination (14, 69–73). Therefore, UFC should not be considered an adequate screening test for SH and should be used in combination with other tests or in specific populations (1, 14).

Several authors reported the presence of an altered circadian cortisol secretion rhythm in AI patients with high midnight cortisol levels (22, 44, 48, 56, 60). Even if midnight serum cortisol (MSeC) has been shown to be a promising tool for diagnosing SH (22), its use is limited by the need of the hospital admission for the cumbersome procedure, and it could be used as a confirmative test in selected patients (60). The possible use of midnight salivary cortisol (MSaC), which is more feasible and less expensive, is still debated (73, 74). Some authors found a low sensitivity of MSaC in identifying SH (31, 32), whereas others showed that subjects with either consistent or frequent elevations of this parameter may actually have SH (69). In fact, the various studies on the diagnostic accuracy of the different salivary cortisol assays are hardly comparable for differences in the patients' and controls' selection criteria and in the diagnostic performance and sample collection techniques of the various laboratory methods (75). Thus, this test should not be used for diagnosing SH until further studies and a standardization of the laboratory methods are available.

Low serum ACTH levels are frequently found in AI patients (19, 21, 32, 36, 40, 43, 44, 48, 49, 56, 60, 61). Because ACTH is generally low in patients with ACTH-independent overt cortisol excess (14), this parameter has also been proposed for diagnosing SH (1, 9, 39). However, because ACTH may be normal even in patients with ACTH-independent overt cortisol excess, the role of low ACTH levels in diagnosing SH is questioned (23). Therefore, ACTH alone does not seem sensitive enough for diagnosing SH. The determination of ACTH levels after CRH does not seem to add any advantage (1, 23, 34, 35, 37, 38, 46) to screening for SH. However, measuring basal and CRH-stimulated ACTH levels in AI patients with established SH helps to avoid missing a possible ACTH-dependent origin of the cortisol excess. Indeed, monolateral or bilateral adrenal enlargement is frequent in patients with an ACTH hypersecretion. Therefore, in AI patients with a strong suspicion of cortisol excess, even if subclinical, the presence of not suppressed basal ACTH levels should push the clinician to exclude the presence of a pituitary or ectopic ACTH hypersecretion. In particular, ACTH levels above 20 pg/ml (4.4 pmol/liter) or below 10 pg/ml (2.2 pmol/liter) suggest an ACTH-dependent or -independent cause of SH, respectively (66). A CRH-stimulated ACTH determination is useful in those subjects with baseline ACTH levels between 10 and 20 pg/ml (2.2–4.4 pmol/liter). In these patients, an ACTH peak below 30 pg/ml (6.6 pmol/liter) after CRH excludes the presence of an ACTH-dependent SH (76).

Low serum DHEAS levels are one of the most frequent HPA axis alterations in AI patients (35–38, 41). Although it may reflect an autonomous ACTH-independent cortisol hypersecretion, available data do not demonstrate that low DHEAS concentration is a reliable index of SH (1, 23, 35), also considering that DHEAS levels decrease with age (77).

Because the increase in sensitivity is accompanied by the decrease in specificity with the lowering of the 1-mg DST cutoff and vice versa, the combination of different parameters of HPA axis activity has been proposed to increase specificity without affecting sensitivity. In a seminal paper, Terzolo *et al.* (42) proposed the use of different combinations of several different parameters (*i.e.* high UFC levels, cortisol levels after 1-mg DST, high average daily serum cortisol, altered circadian cortisol rhythm, low basal ACTH levels, or blunted ACTH response to CRH) to screen for SH and the terms "definitive SH," "probable SH," and "possible SH". To simplify the diagnostic workout, other authors used the concomitant presence of at least two altered parameters of HPA axis activity for SH diagnosis (9, 18, 19, 21, 32, 37, 39, 40, 42, 47, 49, 52–54, 56, 60, 61).

Diagnostic accuracy of the different approaches for diagnosing SH

A few studies (summarized in Table 2) evaluated the sensitivity and specificity of the different HPA axis parameters or combination of parameters for diagnosing SH. The difficulty in performing such studies is due to the lack of a clinical, biochemical, or functional parameter that can be used as the gold standard. Some studies evaluated the diagnostic accuracy of the various parameters of HPA axis secretion using arbitrarily defined biochemical criteria (9, 31, 32, 52) as the gold standard. Overall, in these studies, the different parameters showed a good specificity (90–98%, using 1-mg DST) but, generally, a poor sensitivity (41–86% using ACTH levels). The altered circadian rhythm, evaluated by either MSaC or MSeC, and UFC levels were not found to be sensitive enough for diagnosing SH (31, 32). However, these results have been biased by the fact that the biochemical gold-standard criteria used to define SH had not been previously validated.

To overcome this limitation, some studies investigated the accuracy of 1-mg DST for diagnosing SH in AI patients using the unilateral concordant uptake of radiotracer by iodocholesterol scintigraphy as the gold standard (48, 67). Using the highest cutoff [5 μg/dl (138 nmol/liter)], 1-mg DST was confirmed to have good specificity (83–100%)

TABLE 2. Accuracy of HPA axis secretion parameters in diagnosing SH

First author, year (Ref.)	No. of patients	CCR (SN/SP)	ACTH (SN/SP)	UFC (SN/SP)	DST (SN/SP)	DEX dose, DST cutoff	Gold standard criteria for SH diagnosis
Mantero, 2000 (9)	1004	43/83	79/85	76/88	73/90	1 mg, 5 μg/dl	≥2 out of CRH, CCR, ACTH, UFC, DST
Libè 2002 (52)	64	n.a.	41/96	33/96	91/98	1 mg, 5 μg/dl	≥2 out of CRH, CCR, ACTH, UFC, DST
Masserini, 2009 (32)	103	22.7/87.7	86.4/59.3	31.8/92.6	86.4/96.3	1 mg, 3 μg/dl	≥2 out of DST, ACTH, UFC
Nunes, 2009 (31)	48	77/69[a]	n.a.	n.a.	n.a.	1 mg, 2.2 μg/dl	DST plus ACTH or CCR
		77/68[b]				1 mg, 2.2 μg/dl	DST plus ACTH or CCR
Barzon, 2001 (67)	83	n.a.	n.a.	n.a.	44/100	1 mg, 5 μg/dl	Norcholesterol scintigraphy
					75/72	1 mg, 1.8 μg/dl	Norcholesterol scintigraphy
Valli, 2001 (48)	31	n.a.	n.a.	n.a.	58/83	1 mg, 5 μg/dl	Norcholesterol scintigraphy
					63/75	1 mg, 3 μg/dl	Norcholesterol scintigraphy
					100/67	1 mg, 2.2 μg/dl	Norcholesterol scintigraphy
Eller-Vainicher, 2009 (58)	60	64.1/81[d]	64.1/38	48.7/81	33.3/85.7	1 mg, 5 μg/dl	Postsurgical hypocortisolism
					59/52.4	1 mg, 3 μg/dl	Postsurgical hypocortisolism
					79.5/23.8	1 mg, 1.8 μg/dl	Postsurgical hypocortisolism
Morelli, 2010 (59)	231	n.a.	52.4/60.5	42.9/80	23.8/93.3	1 mg, 5 μg/dl	Prevalence of complications[e]
					52.4/81.4	1 mg, 3 μg/dl	Prevalence of complications[e]
					71.4/49.5	1 mg, 1.8 μg/dl	Prevalence of complications[e]
Eller-Vainicher 2010 (60)	55	65.2/65.6[c]	n.a.	n.a.	21.7/96.9	1 mg, 5 μg/dl	Metabolic improvement after surgery[f]
					91.3/56.3	1 mg, 2.0 μg/dl	Metabolic improvement after surgery[f]

CRH, Blunted response to CRH; CCR, altered circadian cortisol rhythm (elevated MSeC or MSaC levels); ACTH, low ACTH levels [<10 pg/ml (2.2 pmol/liter)]; UFC, 24-h UFC levels above the upper limit of the normal range; DST, reduced cortisol suppression after a DST; DEX, dexamethasone; n.a., data not available; SN, sensitivity (%); SP, specificity (%).

[a] MSaC levels [cutoff, 1.7 μg/liter (47 nmol/liter)].

[b] MSeC levels [cutoff, 4.9 μg/dl (135 nmol/liter)].

[c] MSeC [cutoff, 4.0 μg/dl (110 nmol/liter)].

[d] MSeC [cutoff, 5.4 μg/dl (149 nmol/liter)].

[e] Concomitant presence of vertebral fractures, arterial hypertension, and type 2 diabetes mellitus.

[f] Improvement after surgery of at least two out of the following possible complications of SH: blood pressure, fasting glucose, body weight, and cholesterol levels.

but low sensitivity (44–58%). However, if the lowest cutoffs were used [1.8 and 2.2 μg/dl (50 and 60.6 nmol/liter), respectively], specificity decreased to 67–72%, whereas sensitivity increased to 75–100% (48–62, 64–67). The 1-mg DST cutoff of 3.0 μg/dl (83 nmol/liter) showed the best compromise between sensitivity (63%) and specificity (75%) (48). The main pitfall of these studies is that the increased uptake of the radiotracer may simply reflect the presence of enlarged adrenal tissue rather than an increased cortisol secretion (1, 35, 78). Because this technique is expensive, time-consuming, and not widely available, it should be reserved for patients with still discordant biochemical data after an adequate follow-up (79, 80).

Another approach to validate the biochemical criteria for SH may be based on the association between the parameters of HPA axis activity and the clinical features of the patients with possible subtle cortisol excess. The occurrence of hypocortisolism after the removal of an adrenal adenoma has been proposed as the gold standard for diagnosing SH (58). In a study of 60 AI patients, we evaluated the accuracy of the HPA axis secretion parameters measured before surgery in predicting the occurrence of postsurgical hypocortisolism (58). We found that the simultaneous presence of elevated UFC and MSeC levels [>5.4 μg/dl (149 nmol/liter)] before surgery had a 100% specificity for predicting postsurgical hypocortisolism, but at the expense of a 30.8% sensitivity. Also in this study, lowering the cutoff of 1-mg DST was demonstrated to lead to a reduction in specificity (from 85.7 to 23.8%) and an increase in sensitivity (from 33.3 to 79.5%). Moreover, after excluding MSeC, all combinations of the remaining parameters did not show enough reliability for predicting hypocortisolism after surgery, and conversely, the normality of all parameters of HPA axis activity before surgery could not rule out with 100% probability the appearance of postsurgical adrenal insufficiency. The main criticism to this approach for diagnosing SH is that postsurgical hypocortisolism reflects only the pituitary sensi-

tivity to cortisol excess and not that at the peripheral tissues (25–30).

Another clinical approach to validate the different criteria for diagnosing SH is to evaluate their association with the simultaneous presence of the possible complications of cortisol excess such as osteoporosis, diabetes mellitus, and hypertension. In the study by Morelli *et al.* (59) on 231 AI patients, the presence of a combination criterion characterized by the presence of at least two biochemical alterations among 1-mg DST above 3 μg/dl (83 nmol/liter), elevated UFC, and ACTH below 10 pg/ml (<2.2 pmol/liter) (DST-UFC-ACTH combination criterion) showed the best balance between sensitivity (61.9%) and specificity (77.1%), reaching an acceptable accuracy (75.8%) in predicting the cluster of complications. This study confirmed the low sensitivity and specificity of 1-mg DST when the high or low cutoff, respectively, is used and the low accuracy of the reduced ACTH and increased UFC level, when used as single criterion (59). The limit of this approach is that these complications (*i.e.* osteoporosis, diabetes mellitus, and hypertension) are not specific for cortisol excess, being highly prevalent in the general population. Moreover, the use of the DST-UFC-ACTH combination criterion is limited to the diagnosis of SH of adrenal origin because ACTH levels are useless in patients with suspected ACTH-dependent SH.

In a recent retrospective study, we tested in surgically (n = 55) or conservatively (n = 33) treated AI patients the accuracy for diagnosing SH of various HPA axis parameters using the changes in blood pressure, cholesterol levels, body weight, and fasting glucose after AI removal as the possible gold standard for defining SH (60). The DST-UFC-ACTH combination criterion was confirmed to be useful because it showed the best accuracy in predicting improvement (sensitivity, 65.2%; specificity, 68.8%) in surgically treated patients and worsening of the endpoints (sensitivity, 55.6%; specificity, 82.9%), in the conservatively treated subjects.

In summary, all studies specifically designed for individuating the best criterion for diagnosing SH showed that no single parameter has, in fact, an adequate sensitivity and specificity. In the absence of a clear and widely accepted gold standard and of more reliable methods for assessing cortisol secretion (particularly for the ACTH and UFC measurement), the diagnosis of SH remains a challenge for physicians. However, to date, the DST-UFC-ACTH combination criterion seems the best compromise to diagnose SH because it has been validated on a clinical basis (32, 59, 60).

Prevalence of SH and of Its Different Causes

Several studies suggest that SH is likely to be underreported. It is known that diabetes mellitus and osteoporosis are frequently found in patients with cortisol excess. Because in past years several studies have shown that SH may also be associated with a high risk of osteoporotic fractures and metabolic consequences (15–22), it has been hypothesized that in populations of diabetic and osteoporotic patients the prevalence of SH would be higher than in healthy subjects (Table 3).

In a cross-sectional study on 90 obese diabetic patients with poor metabolic control, Leibowitz *et al.* (63) found a 3.3% prevalence of SH due to an adrenal adenoma in one patient and a pituitary adenoma in two patients using 1-mg DST above 5.1 μg/dl (140 nmol/liter) as a screening test. This finding was confirmed in a study showing the presence of one case of pituitary SH in a sample of 48 overweight diabetics (81). In a larger study of a similar population using 1-mg DST as a screening test with a lower and, therefore, more sensitive cutoff, SH was ascertained in four (three of pituitary and one of adrenal origin) of 200 diabetic patients studied (2.0% prevalence) (82).

TABLE 3. Studies investigating the prevalence of SH and its origin in type 2 diabetic and osteoporotic patients

First author, year (Ref.)	Population (n)	Screening test	Cutoff	Overall prevalence (%)	Adrenal origin (%)	Pituitary origin (%)	Other origin (%)
Leibowitz, 1996 (63)	Type 2 diabetics (90)	1-mg DST	5.1 μg/dl	3.3	33.3	66.6	0
Contreras 2000 (81)	Type 2 diabetics (48)	UFC	112 μg/24 h	2.1	0	100	0
		1-mg DST	1.4 μg/dl				
Kann, 2001 (90)	Osteoporotics (78)	3-mg DST	1.8 μg/dl	3.8	100	0	0
Catargi, 2003 (82)	Type 2 diabetics (200)	1-mg DST	2.1 μg/dl	5.5	72.3	27.3	0
Chiodini, 2005 (83)	Type 2 diabetics (294)	1-mg DST	1.8 μg/dl	10.8	66.6	13	20.4
Liu, 2005 (88)	Type 2 diabetics (154)	MSaC	0.15 μg/dl	0	0	0	0
Reimondo, 2007 (85)	Type 2 diabetics (100)	1-mg DST	3.6 μg/dl	1	0	100	0
Chiodini, 2007 (91)	Osteoporotics (147)	1-mg DST	1.8 μg/dl	4.8	85.4	14.6	0
Newsome, 2008 (86)	Type 2 diabetics (178)	1-mg DST	1.8 μg/dl	0	0	0	0
Taniguchi, 2008 (84)	Type 2 diabetics (77)	MSeC	5.0 μg/dl	2.6	0	100	0
Mullan, 2010 (87)	Type 2 diabetics (201)	MSaC	0.4 μg/dl	0	0	0	0

UFC, 24-h UFC. SI conversion factor: cortisol × 27.56.

However, SH was very likely in seven additional subjects. Overall in this study, the prevalence of SH could be estimated to be almost 5.5%, with a pituitary and adrenal origin of 1.5 and 4.0%, respectively. These data were confirmed in a similar controlled study on 294 diabetic inpatients in whom a 10.8% prevalence of SH was found, with pituitary, adrenal, and undefined/ectopic origin accounting for 1.4, 7.2, and 2.2%, respectively (83). In keeping with this, Taniguchi *et al.* (84) found a 2.6% prevalence of SH in a sample of 77 inpatients with type 2 diabetes. Diagnosis was done by measuring MSeC using a cutoff of 5 μg/dl (138 nmol/liter). However, these figures were partially different in the study of Reimondo *et al.* (85), in which only one of 100 patients with newly diagnosed diabetes was found to have a pituitary-dependent SH. In this study, however, a high cutoff for 1-mg DST was used.

Other authors failed to detect patients with SH in the populations at risk (86–88). By using 1-mg DST as a screening test with a low cutoff in a sample of 178 diabetic patients, Newsome *et al.* (86) did not find any subject with SH. Similarly, by using MSaC, a poor test for screening SH, two studies did not detect SH in more than 150 overweight/obese diabetic patients (87, 88). Besides the different cutoffs or screening tests used, these discordances may be related to the different populations studied (*i.e.* outpatients or inpatients, patients with poorly or well-controlled diabetes).

An unexpected high prevalence of SH has also been reported in patients with osteoporosis. Indeed, it is well known that vertebral fractures may be the presenting symptoms of an otherwise asymptomatic cortisol excess, and several case reports have been reviewed recently (89). However, data regarding the prevalence of SH in osteoporosis are scarce. In assessing the HPA axis by 3-mg DST with a sensitive cutoff, a 3.8% prevalence of SH was found; all cases were of adrenal origin (90). A subsequent study from our group on more than 200 patients using the same screening test showed that SH was present in 4.8% of patients with osteoporosis and 10.8% of patients with osteoporosis and vertebral fractures. In this study, SH was of adrenal and pituitary origin in 4.1 and 0.7% of patients, respectively (91).

These studies suggest that SH may be more frequent in patients with diabetes and osteoporosis, thus explaining the increased fracture risk. Moreover, in reducing the cutoff of the screening test and therefore increasing its sensitivity, the adrenal cause of SH became more frequent than the pituitary cause. Overall, from the available data regarding the screening of the population at risk for SH (diabetics and osteoporotics), it comes evident that, unlike the condition of overt cortisol excess, the condition of SH is more commonly of adrenal origin. However, no data are available regarding the prevalence of subclinical ACTH hypersecretion in patients with pituitary incidentalomas (92).

The usefulness of the screening of SH in the populations at risk clearly depends on the possible SH-associated increased morbidity and mortality, which are still unknown. Moreover, because the *a priori* possibility of having SH is estimated to be lower than that of a false-positive result (1), the economic costs of the screening for SH would probably be elevated. To date, no data are available on the cost effectiveness of the screening of the populations at risk. However, it seems rational to screen for SH all patients with very low bone mineral density and/or vertebral fractures without other known secondary causes of osteoporosis (91) and type 2 diabetes patients with poor metabolic control despite an adequate diet, lifestyle, and pharmacological treatment—in particular those simultaneously affected with osteoporosis and hypertension (59).

Therapy of SH

The available studies regarding the clinical effects of the recovery from SH considered the improvement of its possible metabolic consequences (*i.e.* diabetes, hypertension, and obesity) as endpoints (18, 46, 54, 61, 93–97). Unfortunately, to date, no large prospective randomized trial compared the effect of surgical *vs.* conservative treatment in patients with SH (Table 4). The only available prospective randomized study found in 23 surgically treated subjects improvement of hypertension, diabetes, obesity, and dyslipidemia in 66.7, 62.5, 50, and 37.5% of cases, respectively (57). On the contrary, in 22 conservatively treated patients, hypertension, diabetes, and dyslipidemia worsened in 80, 33.3, and 20% of cases (57). However, in this study, a direct comparison of the changes of the endpoints between the two groups was not done. Nonetheless, as observed by the authors, these data suggest that surgical treatment is more beneficial than conservative treatment (57).

In keeping with these data, previous prospective, nonrandomized studies found similar results (18, 46, 54, 93–96). Rossi *et al.* (18) found that blood pressure and diabetes improved in 100 and 60% of five surgically treated SH patients, respectively, whereas no changes were seen in seven conservatively treated SH subjects. A subsequent study of 10 subjects found after recovery from SH an improvement of blood pressure, metabolic control of diabetes, and dyslipidemia in 83, 22, and 67% of cases, respectively, whereas in 12 conservatively treated subjects, hypertension, diabetes, and obesity worsened in 17, 25, and 17% of cases, respectively (96). Several small studies suggested the improvement of blood pressure (54, 93, 95),

TABLE 4. Studies investigating the effect of the recovery from SH on blood pressure, body weight, fasting glucose, and bone

First author, year (Ref.)	Design	SH+ Surg (n)	SH+ Cons (n)	SH− Surg (n)	SH− Cons (n)	FU (months)	SH criteria	BP	BW	FG	Bone
Rossi, 2000, (18)	Prosp.	5	7	13	25	18–300	Cortisol >5.0 μg/dl after 1-mg DST plus 1 out of: high UFC, low ACTH, loss of F rhythm, blunted ACTH after CRH	↑[a]	–	↑[a]	–
Midorikawa, 2001 (46)	Prosp.	4	–	8	–	1	Cortisol >3.0 μg/dl after 1-mg DST and low ACTH	↕[a]	↓	↑[a]	–
Emral, 2003 (54)	Prosp.	3	1	3	57	n.a.	Cortisol >3.0 μg/dl and UFC reduction < 50% after 3-mg DST	↑	↑	↑	–
Bernini, 2003 (93)	Prosp.	6	–	9	–	12	Cortisol >5.0 μg/dl after 1-mg DST	↑[a]	↓	↑[a]	–
Erbil, 2006 (94)	Retrosp.	11	–	–	83	12	Cortisol >3.0 μg/dl after 1-mg DST and 8-mg DST	↕	↕	↕	–
Mitchell, 2007 (95)	Retrosp.	9	–	–	–	1–30	Cortisol >1.0 μg/dl after 1-mg DST plus 1 out of: high UFC, low ACTH, low DHEAS, lateralization with AVS, clinical signs	↑	↑	↑	–
Tsuiki, 2008 (96)	Retrosp.	10	12	–	–	7–19	Cortisol >3.0 μg/dl after 1-mg DST and ≥1.0 μg/dl after 8-mg DST plus 1 out of: low ACTH, loss of CCR, low DHEAS, AS uptake	↑	↓	↕	–
Toniato, 2009 (57)	Prosp. Rand.	23	22	–	–	24–204	Cortisol >5.0 μg/dl after 1-mg DST plus 1 out of: high UFC, low ACTH, loss of CCR rhythm, blunted ACTH after CRH	↑	–	↕	↓
Sereg, 2009 (97)	Retrosp.	5	8	42	70	109 ± 37	Cortisol >3.6 μg/dl after 1-mg DST and/or MSeC >5 μg/dl	↓	↓	↓	–
Chiodini, 2010 (61)	Retrosp.	25	16	30	37	18–54	2 out of: cortisol >3.0 μg/dl after 1-mg DST, low ACTH, high UFC	↑[a]	↑	↑	–

SH+, Patients with SH; SH−, patients without SH; FU, range of follow-up; Surg, number of surgically treated patients; Cons, number of patients followed up with conservative approach; BP, blood pressure; BW, body weight; FG, fasting glucose; CCR, altered circadian cortisol rhythm (elevated MSeC or MSaC levels); low ACTH, ACTH levels <10 pg/ml; high UFC, 24-h UFC levels above the upper limit of the normal range; DST, reduced cortisol suppression after a DST; Prosp., prospective; Retrosp., retrospective; Rand, randomized; Cortisol, serum cortisol; AVS, adrenal vein sampling; AS, adrenal scintigraphy; n.a., not available; ↑, improvement; ↕, possible improvement; ↓, stable; –, not evaluated. SI conversion factors: cortisol × 27.56; ACTH × 0.22.

[a] Improvement also in SH-treated subjects.

glucose metabolism (46, 54, 93, 95), and body weight (54, 95) in surgically treated SH patients. In a retrospective, nonrandomized study, we reported that in 25 surgically treated SH patients, body weight, blood pressure, and glucose levels improved (32, 56, and 48%, respectively) more frequently than in untreated SH subjects (12.5, 0.0, and 0.0%, respectively) (61). On the contrary, in surgically untreated SH patients, blood pressure, glucose, and cholesterol levels worsened more frequently (50.0, 37.5, and 50.0%, respectively) than in surgically treated patients (0, 0, and 24%, respectively) (61). Although surgically treated patients were younger than conservatively treated

patients, the modification of the metabolic endpoints was independent of age as well as the presence of hypertension, diabetes, obesity, and dyslipidemia at baseline (61). At variance with all the above-mentioned studies, a recent retrospective study found no difference in hypertension, diabetes, and obesity between five and eight SH patients surgically and conservatively treated, respectively (97). However, it is likely that the high number of patients who refused to participate in this study have introduced a crucial selection bias.

Importantly, the criteria for defining an improvement of the possible complications of SH have been different among the different studies and were not always reported. In our study (61), the improvement or worsening of blood pressure and fasting glucose was defined following the Guidelines for the Management of Arterial Hypertension of the European Society of Cardiology and the Adult Treatment Panel III (ATP III) criteria, respectively, regardless of the diagnosis of hypertension or diabetes before or after surgery. Importantly, studies using similar criteria were able to show a clear positive effect of surgery on the metabolic consequences of SH (18, 54, 61, 93, 96, 97). On the contrary, in those studies in which these criteria were not used and the endpoint was simply the presence of hypertension or diabetes before and after surgery, the effect of recovery from SH on its metabolic consequences was less impressive (94) or absent (97). Therefore, summarizing the available data, it is likely that in all patients with SH, and particularly in those with possible SH complications, surgical treatment may be advantageous. However, to date, the small sample size of the available studies and the lack of a large prospective randomized trial could not allow us to draw any firm conclusion about this point.

Few studies evaluated the accuracy of the SH diagnosis before surgery to predict the improvement after surgery and, therefore, to address the treatment of choice in the individual subject (18, 46, 61, 93). This is of utmost importance because in several studies some of the surgically treated patients without SH experienced improvement of some metabolic endpoints (18, 46, 61, 93). It is possible to hypothesize that some patients classified as not having SH had, in fact, a mild degree of cortisol hypersecretion, suggesting that the diagnosis of SH had not been sensitive enough.

Looking to the above-mentioned retrospective data on 55 surgically treated patients with AI (60), 1-mg DST greater than 5 μg/dl (138 nmol/liter) and less than 2 μg/dl (55 nmol/liter) had the best specificity and sensitivity (96.9 and 91.3%, respectively) for identifying patients that may improve after surgery. In patients with 1-mg DST between these values, the presence of MSeC greater than 4.0 mg/dl (110 nmol/liter) or ACTH less than 10.0 pg/ml (2.2 pmol/liter) combined with the presence of at least two metabolic complications before surgery had a 76% accuracy in predicting improvement. Using the protocol illustrated in the study, in more than 80% of cases the improvement after surgery was correctly predicted before surgery (60). This study clearly suffers from the limits of the small sample and of its retrospective and nonrandomized design. However, it suggests that by combining clinical and biochemical parameters, it could be possible to identify which AI patient may benefit from surgery.

In the last few years, several non-ACTH factors have been suggested as possible regulators of steroidogenesis in adrenal adenomas. Indeed, it has been shown that receptors for several ligands are abnormally expressed at the membrane of tumoral adrenocortical cells, such as those for glucose-dependent insulinotropic peptide, catecholamine, vasopressin, serotonin, angiotensin II, leptin, and LH/human chorionic gonadotropin (98–100). Because these aberrant receptors may be specific pharmacological targets for controlling cortisol secretion, their detection deserves particular interest and some protocols have been developed (99). Indeed, somatostatin analogs have been used to control food-dependent cortisol hypersecretion due to the presence of aberrant glucose-dependent insulinotropic peptide receptors (100, 101); propranolol has been proposed in patients with adrenal hypercortisolism (102) and leuprolide acetate in LH-dependent Cushing's syndrome (103). In the future, these pharmacological approaches may become extremely useful, in particular in SH patients with bilateral adenomas because in these subjects the excision of the predominant mass is often not sufficient to control the cortisol excess.

Follow-up of patients with SH

To date, no widely accepted guidelines are available regarding the most adequate follow-up in patients with possible or ascertained SH who did not undergo surgery. The difficulties in defining a protocol are related to the variability of cortisol secretion in these patients (3, 22) because even a 2-yr follow-up may be too short to ascertain the presence of SH (79). On the other hand, definitive data about the risk of transformation of nonfunctioning nodules to functional tumors are lacking. Although this risk was reported to be low in patients with adrenal adenomas smaller than 3 cm (3), two studies suggested that in patients with an adrenal mass more than 2 cm in size, the estimated cumulative risk of developing SH may vary between 7 and 47% after 5 yr (50, 52). Until data will be available from large prospective studies, a reasonable approach may be to repeat the hormonal screening annually for 5 yr, measuring 1-mg DST, ACTH, and UFC levels,

particularly in patients with possible or not clearly ascertained SH.

Similarly, because in some patients with SH not operated on, bone mineral density, fasting glucose, blood pressure, and cholesterol levels have been shown to worsen during follow-up (49, 61), a careful monitoring of these complications and an evaluation of the adequacy of the medical therapy should be performed annually. In the presence of a worsening of bone status, and/or hypertension, and/or diabetes despite adequate treatments, or in the presence of an increase of cortisol secretion, surgery is a reasonable option.

Conclusions

Based on the data reported above, it becomes clear that no agreement exists regarding how to biochemically diagnose SH. This is due to the lack of a clinical or functional parameter to be used as the gold standard to test the diagnostic accuracy of the available biochemical parameters. Moreover, to date, methodological problems exist in reliably measuring cortisol secretion. If a clear diagnosis of SH cannot be made, it is difficult to ascertain the effect of surgery. Some improvements attributed to surgery could, in fact, have been related to nonspecific changes in medical treatment/lifestyle and not to the previous surgery. These uncertainties, in turn, bring into question the real clinical importance of SH itself and the need of a surgical treatment in these patients instead of the optimization of medical therapy (61). Indeed, in patients with SH the optimization with strict criteria of the medical treatment of osteoporosis, hypertension, diabetes, and dyslipidemia may avoid the development of the clinical consequences of these complications (*i.e.* fractures, cardiovascular diseases, *etc.*). Although no studies have investigated the association of SH with "hard" endpoints, such as cardiovascular morbidity and mortality, the available data suggest a possible deleterious role of SH, at least on glucose and bone metabolism and on hypertension, even in patients adequately followed up with antihypertensive and antidiabetic medical therapy (61). Moreover, it must be considered that the optimization of the medical therapy is not completely free of adverse events and that adrenal surgery is becoming increasingly safer by endoscopic procedures. Finally, because patients with SH seem to worsen if not surgically treated, the economic costs of surgery have to be compared with those of curing the possible consequences of SH (*i.e.* chronic complications of diabetes and hypertension, and fractures). In this regard, however, the major issue is that if SH is present, at least, in 0.2% of the population, many more adrenal operations will be necessary than those currently performed. Therefore, a benefit stratification before surgery will need to be accurate.

These considerations point to the need of large, prospective, randomized trials investigating the effect of surgery on the improvement or worsening of the possible complications of SH. These studies should include both surgically treated and adequately medically treated patients with and without SH and should provide for an adequate follow-up period (at least 3–5 yr). Several surrogate endpoints, such as body weight, blood pressure, cholesterol, and glucose or glycated hemoglobin (HbA1C) levels should be measured. The improvement or worsening of body weight should be defined by a greater than 5–10% decrease or increase, respectively (104). The improvement or worsening of arterial blood pressure should be defined if the nonhypertensive patients pass from a prehypertension category to another or the hypertensive patients from a hypertension grade to another, following the Guidelines for the Management of Arterial Hypertension of the European Society of Cardiology (105), or if the antihypertensive drugs must be reduced/stopped or increased to maintain the therapeutic target, respectively. Fasting total cholesterol and/or low-density lipoprotein levels should be considered to be improved if they show a 25 or 30% reduction, respectively (106), or worsened if they passed from a category to another in agreement with the ATP III criteria (107). In patients with diabetes, the improvement/worsening of the glycometabolic control should be defined by the reduction/increase of at least a percentage point of HbA1C and/or by the achievement/loss of the recommended targets [HbA1C $<7\%$; preprandial capillary plasma glucose between 70 and 130 mg/dl (3.9–7.2 mmol/liter); peak postprandial plasma glucose <80 mg/dl (10 mmol/liter] or if the antidiabetic drugs must be reduced/stopped or increased (108). In patients without diabetes, the therapeutic targets should be a HbA1C below 6.5%, a fasting plasma glucose level below 100 mg/dl (5.6 mmol/liter), and a plasma glucose value after a 75-g oral glucose tolerance test below 140 mg/dl (7.8 mmol/liter) (108). The improvement/worsening of bone mineral density should be defined in the presence of at least a 3.5% increase/decrease during the follow-up period (109).

Moreover, studies with an even longer follow-up (*i.e.* 10 yr) could evaluate the effects of the surgical or conservative approach not only on these surrogate endpoints but also on the "hard" endpoints, such as the incidence of major cardiovascular events, vertebral fractures, the appearance or progression of diabetic complications, mortality, and quality of life. To evaluate this latter parameter, a specifically designed questionnaire for patients affected with cortisol excess should be used.

Finally, to reduce the number of useless adrenal operations, these studies should also extensively and regularly (*i.e.* annually) evaluate the HPA axis activity in AI patients. These data could provide important information regarding the most accurate biochemical parameters in predicting before surgery the benefit of surgery itself. For these reasons, more reliable methods for measuring cortisol secretion are also needed.

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